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No. 06-1249

In The Supreme Court of the United States

WYETH,

Petitioner,

v.

DIANA LEVINE,

Respondent.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SUPREME COURT OF VERMONT

BRIEF OF DES ACTION AS *AMICUS CURIAE* IN SUPPORT OF RESPONDENT

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INTEREST OF THE AMICUS CURIAE[1]

DES Action is a national, non-profit organization of over two thousand members from all fifty states. Its purpose is to provide education and support for the two and one-half million daughters and sons exposed *in utero* to diethylstilbestrol ("DES"), a synthetic estrogen approved by the Food and Drug Administration ("FDA") and prescribed to pregnant women between 1948 and 1971 for the prevention of miscarriage. DES was approved by the FDA and promoted by dozens of manufacturers for over two decades as a miscarriage preventative without a single controlled study demonstrating its efficacy or safety in animals or humans. Today, the FDA, the National Institutes of Health, the Centers for Disease Control, and the World Health Organization unanimously agree that the use of DES in pregnancy is of no value in preventing miscarriage and that DES is a transplacental carcinogen and teratogen.

For over thirty years, DES Action has represented the DES-exposed, both in the United States and internationally, by creating, maintaining, and providing a repository of health information, a list of DES-knowledgeable healthcare providers across the country, counseling and support groups, and advocating for research into the effects of DES.

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[1] The parties have consented to the filing of this *amicus* brief. Pursuant to Rule 37.6, this *amicus* states that this brief was not authored in whole or in part by counsel for any party, and that no person or entity other than this *amicus* and its counsel made a monetary contribution to the preparation or submission of this brief.

DES Action communicates with its members and with the DES-exposed through its website and associated chat groups, through its newsletter, and by events open to members and the public. Thousands each year contact DES Action for information and guidance regarding their DES injuries by phone, letter, or through DES Action's website, www.desaction.org.

DES Action files this *amicus* brief to protect the legal rights of the hundreds of DES daughters, sons, and grandchildren yet to realize or manifest their DES injuries and yet to seek compensation for their injuries and malformations from their exposure *in utero* to DES. The teratogenic effects of *in utero* DES exposure often take decades to manifest. Each year since 1971, when the connection between *in utero* DES exposure and vaginal cancer was made and the FDA, under pressure from Congress, declared it contraindicated for pregnant women, the medical literature reports new adverse manifestations of DES exposure and DES injuries. Recently it has been found that DES daughters have an increased risk of breast cancer. See, e.g., Julie R. Palmer, et al., "Prenatal Diethylstilbestrol Exposure and Risk of Breast Cancer," 15 Cancer, Epidemiology, Biomarkers & Prevention 1509 (2006). Many DES daughters, having waited until their thirties or forties to have children, are only now discovering obstacles to fertility from their DES-malformed reproductive tracts; others will develop cervical and vaginal DES-related cancer in the future. Should unconditional or blanket pre-emption be declared by this Court, DES victims shall be without compensation for their infertility, cancer,

preterm births, ectopic pregnancies, and other DES-caused injuries.

SUMMARY OF ARGUMENT

This *amicus* asks the Court to deny the position of Petitioner and its *amici* and affirm the Supreme Court of Vermont, rejecting blanket pre-emption in pharmaceutical cases. The briefs of Petitioner and its *amici*, most notably the brief of the United States, advocate that the FDA's balancing of risks and benefits weighs in favor of blanket pre-emption without conditions. All now agree that the FDA should never have approved DES for use in pregnancy, and that it should have been taken off the market decades before the hue and cry from Congress forced the FDA to act. See Hearing Before the Subcommittee on Government Operations 92nd Congress Nov 11, 1971.

This amicus opposes the concept that FDA approval of a drug unconditionally pre-empts state law tort claims. DES is, this *amicus* believes, the most telling example of a bureaucratic error by the FDA in its history. The FDA's mission of scrutiny and supervision of drug manufacturers and their economic incentives to over-promote drugs was completely suspended. The DES experience reveals that pre-emption would make no distinction between passive and active FDA enforcement; no difference between a manufacturer following federal regulations and a manufacturer flouting them; no difference between a drug still in its experimental phases and a drug "generally recognized as safe" for decades; no difference between a drug that is

subjected to the rigorous examination and give and take of its therapeutic index and one that is summarily and cursorily rubber-stamped; no difference between the drug in the current FDA approval process and a drug approved by the FDA sixty years ago. Blanket pre-emption would cast too wide a net.

FDA pre-emption is not appropriate when, as with DES, animal and human studies regarding safety were omitted from consideration, clinical trials were never required by the FDA, and the only controlled, double-blind study conducted revealed DES to be ineffective for eighteen years before its recall. When the FDA's review of a drug is inadequate, either through manufacturer under-reporting, lack of resources, or inadvertence, as all were with DES, there must be a point where the tort system should evaluate a drug company's conduct in exercising due care and prudence to ensure that the safety of their product was unreasonable in accordance with the state of the art at the time. FDA law concerns scientific proof of the efficacy and safety of a drug. Tort law concerns the conduct of the manufacturer. Different interests and perspectives. The FDA's mission is the health of the nation; drug manufacturers are interested in profit for their shareholders.

ARGUMENT

I. THE DES STORY

"For over three decades, doctors prescribed diethylstilbestrol to nearly five million women in the

United States as a way to prevent pregnancy problems such as miscarriage . . . . But the synthetic estrogen also known as DES didn't work." Reeves v. Eli Lilly & Co., 368 F. Supp. 2d 11, 12 (D.D.C. 2005).

DES was synthesized in the 1930's by Sir Charles Dodds, who was seeking a cheap estrogen which could be taken orally; even Dr. Dodds himself did not believe in giving synthetic estrogen to otherwise healthy women. See Barbara Seaman, The Greatest Experiment Ever Performed on Women 36-37 (2003); Roberta Apfel, M.D. and Susan Fisher, M.D., DES and the Dilemmas of Modern Medicine 13 (1984). Because British law did not allow patents on discoveries financed by government grants, the drug was never patented, and as such was sold under a multitude of labels. See id. Estrogens were long known as potential teratogens and carcinogens. See Seaman at 44. By 1939, professors Greene, Burrill, and Ivy of Northwestern University found that the offspring of rodents given DES while pregnant showed significant deformities of their reproductive organs. See R.R. Greene, et al., "Experimental Intersexuality: The Paradoxical Effects of Estrogen on the Sexual Development of the Rat," 74 Anatomical Record 4 (May 1939). Furthermore, DES resists attempts by the body to metabolize or excrete it, and so regular ingestion of DES caused a significant amount of the drug to accumulate in the body. See K.K. Chen, M.D., "The New Synthetic Estrogen, Stilbestrol," Quarterly Bulletin Ind. Univ. Med. Ctr. 15, 16 (April 1941).

In the late forties, favorable reports on DES as an anti-abortifacient were presented and packaged

to the FDA, coordinated by a committee of drug company officials, under the auspices of what would become the American Pharmaceutical Society; this committee pooled favorable research and excluded unfavorable criticism. Not a single drug company performed any independent research, much less a controlled study or clinical trial, to determine the safety and efficacy of DES See Stephen Fenichell and Lawrence S. Charfoos, Daughters at Risk: A Personal D.E.S. History 34-36 (1981).

When DES was first approved, the FDA was evaluating a crush of applications with its new responsibility to test drugs for safety. See FDA, "New Drug Application Approvals and Receipts, Including New Molecular Entities, 1938 to Present," available at http://www.fda.gov/oc/history /NDAapprovals.html (last visited July 23, 2008). Testing for efficacy was not required until 1962. See Thaddeus H. Grasela, Jr., "A Nationwide Drug Surveillance Network," Pharmacoepidemiology 171 (Stanley A. Edlavitch, ed. 1987).

In those days, the FDA had a tiny fraction of its present manpower and resources and could not give DES anywhere near the level of scrutiny that drugs receive today, much less the investigation that it deserved. The FDA did not even require proof of efficacy until 1962, and at that point grandfathered DES for all uses.

In 1947, as the manufacturers of DES were gearing up for FDA approval of DES for use in pregnancy, Dr. Rosenblum, a leading obstetrician and gynecologist of Cedars of Lebanon Hospital in

Los Angeles wrote an editorial requesting that specific investigation be done to determine if DES would cause cancer or hormonal imbalances in the exposed offspring, asking the specific questions:

> 1. Will diethylstilbestrol in large dosages cause pituitary or other glandular imbalance which will become manifest later in life?
>
> 2. Is diethylstilbestrol in such large dosages carcinogenic, and as such unsafe to give even to pregnant women?

See Gordon Rosenblum and Eugene Melinkoff, "Preservation of Threatened Pregnancy With Particular Reference to the Use of Diethylstilbestrol," 55 Western J. of Surgery, Obstetrics, & Gynecology 597 (1947). Neither the drug companies nor the FDA considered these questions, nor did the FDA look outside the submissions to the dozens of reports in the literature critical of DES's efficacy and safety at the time. See Appendix 1. The DES manufacturers relied on cherry-picked studies showing the safety of the new indication. See Fenichell and Charfoos at 51. DES was approved for use in pregnancy on May 25, 1947.

The pregnancy dosage recommendations began at five milligrams, and increased to over one hundred milligrams per day. For purposes of illustration, comparing the current dosage of estrogen in a birth control pill with DES, a pregnant woman on DES was ingesting the estrogenic

equivalent of hundreds of birth control pills daily. See Pat Cody, DES Voices: From Anger to Action 75 (2008). A child *in utero* would essentially bathe in estrogen. At those doses, its developing estrogen-sensitive reproductive organs in their embryonic formation would be over-stimulated and malformed by the excess of hormones. See id.

The FDA, without any consultation with the obstetrical and gynecological community, without any experts in obstetrics and gynecology within the agency, and without the currently employed advisory panels with specialized knowledge of past research in the field, rubber-stamped DES for use in pregnancy. Following DES's introduction as a miscarriage preventative came a cavalcade of critical studies showing the dangers of using DES in pregnancy, which the FDA similarly ignored:

- In 1949, estrogens were found to pass through the placenta in guinea pigs, causing reproductive anomalies in the offspring. See H. Burrows, "Oestrogens," Biological Action of the Sex Hormones (1949).

- In 1950, research into minks fed DES found that DES inhibited their reproduction and caused uterine anomalies in the offspring. See Robert K. Enders, "Mink Production in Relation to Stilbestrol" 16 Fur Journal 7 (1950).

- In 1953, researchers at the University of Chicago undertook the first and only double-blind, controlled study of the efficacy of DES

for prevention of miscarriage. The study found that the women given a placebo had more live births than the women given DES; this study found that DES was ineffective to prevent miscarriages. See W.J. Dieckmann, M.D., et al., "Does the Administration of Diethylstilbestrol During Pregnancy Have Therapeutic Value?" 66 Am. J. Obstetrics & Gynecology 1062 (1953). Other reported studies also concluded that DES was of no value in preventing miscarriage. See, e.g., James Ferguson, "Effect of Stilbestrol on Pregnancy Compared to the Effect of A Placebo," 65 Am. J. Obstetrics & Gynecology 592 (1953).

- In 1959, the United States Department of Agriculture, found DES to be a carcinogen when used in animal feed for chicken and sheep, and banned the use of DES in feed for those animals. See Apfel and Fisher at 14.

- Also in 1959, doctors in Philadelphia reported actual reproductive malformations in DES daughters. See Alfred M. Bongiovanni, et al., "Masculinization of the Female Infant Associated with Estrogenic Therapy Alone During Gestation: Four Cases," 19 J. Clinical Endocrinology and Metabolics 1004 (1959).

- By 1959, enough women had been exposed to DES *in utero* that doctors could have noticed abnormalities in those women's reproductive organs through a simple colposcopic examination; abnormalities appear in up to

sixty percent of all women exposed to DES. See Arthur Herbst, "Vaginal and Cervical Abnormalities After Exposure to Diethylstilbestrol In Utero," 40 Obstetrics & Gynecology 287 (1972). Since the FDA had declared the drug safe in 1952, no one revisited the issue, and pregnant women and their daughters continued to be exposed to DES for an additional twelve years in the face of mounting adverse reports.

- In the early 1960's, the world awoke to the risk of teratogenesis from the use of Thalidomide in pregnancy, alerting the medical community to the danger of prescribing medications during pregnancy. At that time, the scientific community recommended that all drugs given to pregnant women be re-evaluated to determine if they had trans-placental side effects. See, e.g., Frank Moya, M.D. and Virginia Thorndike, M.D., "Passage of Drugs Across the Placenta," 84 Am. J. Obstetrics & Gynecology 1778 (1962). Both the FDA and the manufacturers ignored this warning.

Timelines with the relative studies regarding safety, efficacy, and transplacental capabilities of DES ignored by the FDA are attached as Appendix 1.

Naturally, without the FDA's oversight, the producers of DES made no effort to alert the government or the medical community of the drug's dangers:

> During the period defendants marketed DES, they knew or should have known that it was a carcinogenic substance, that there was a grave danger after varying periods of latency it would cause cancerous and precancerous growths in the daughters of the mothers who took it, and that it was ineffective to prevent miscarriage. Nevertheless, defendants continued to advertise and market the drug as a miscarriage preventative. They failed to test DES for efficacy and safety; the tests performed by others, upon which they relied, indicated that it was not safe or effective. In violation of the authorization of the Food and Drug Administration, defendants marketed DES on an unlimited basis rather than as an experimental drug, and they failed to warn of its potential danger.

Sindell v. Abbott Laboratories, 607 P.2d 924, 926 (Cal. 1980). In fact, drug company promotional literature continued to state that DES was the most effective drug to prevent miscarriage. See, e.g., Eli Lilly and Company, De Re Medica 211 (1953). DES manufacturers recommended the prophylactic use of DES, and even recommended DES to women who had no indications of threatened miscarriage. The only warnings and contraindications for DES required by the FDA prior to 1968 regarded headache and nausea, and after that there was only an indeterminate warning as to some unnamed risk to a fetus without specifying likelihood or severity.

Physicians' Desk Reference 819-20 (23d ed. 1969) A 1967 study by the National Academy of Sciences classified DES as ineffective, below even the class of "probably effective." See Cynthia Orenberg, DES: The Complete Story 123 (1981).

In 1971, two doctors from Massachusetts General Hospital – not the drug companies, not the FDA – broke the news in the New England Journal of Medicine that DES was a carcinogen to the exposed daughters. See Arthur Herbst, et al., "Adenocarcinoma of the Vagina," 284 New Eng. J. Med. 878 (1971). The DES tragedy became front-page news. Only after Congress held hearings on DES did the FDA take action and issue a contraindication for use in pregnancy, resulting in DES's removal from the market. Even then, the FDA, after notification the cancer reports, did nothing for six months. See Fenichell and Charfoos at 92-96, 120. By that time, the Centers for Disease Control estimate that between five and ten million women were exposed to DES. See CDC, "About DES," available at http://www.cdc.gov/des/ consumers/about/index.html (last visited July 21, 2008).

DES has now been specifically recognized by Congress as a public health problem. See, e.g., 105 P.L. 340 (1998) (approving funds for DES research). The Centers for Disease Control has DES education as part of its mission. See CDC, "About DES," http://www.cdc.gov/des/ consumers/about/index.html (last visited August 4, 2008). The National Institutes of Health's National Cancer Institute is similarly tasked with dealing with the fallout of the

DES tragedy. See NIH, "DES: Questions and Answers," http://www.cancer.gov/cancertopics/factsheet/Risk/DES (last visited August 4, 2008).

II. PRE-EMPTION SHOULD NOT BE APPLIED TO CURRENT CLAIMS BASED ON FDA APPROVAL OVER SIXTY YEARS AGO

An agency's decision leads to pre-emption "where it is 'impossible for a private party to comply with both state and federal requirements' . . . or where state law 'stands as an obstacle to the accomplishment and execution of the full purposes and objectives of Congress.'" Sprietsma v. Mercury Marine, 537 U.S. 51, 64 (U.S. 2002) (citations omitted). DES victims were exposed thirty to fifty years ago, when the drug manufacturers could have: 1) strengthened their warnings without seeking prior FDA approval for those changes; 2) the DES manufacturers could have adequately tested the drug and found its dangers without prior FDA approval; 3) the DES manufacturers could have changed their literature to include reports of teratogenesis and carcinogenesis without prior FDA approval; 4) DES manufacturers could have stated in their literature that DES that there had been no adequate controlled testing for safety and efficacy without prior FDA approval; 5) the DES manufacturers could have withdrawn the drug without prior FDA approval or anyone suffering from removal from the market as DES was ineffective. As such, it makes little sense for there to be implied pre-emption based on considerations the FDA did not have at the time of approval.

Before 1962, drugs were not required to be tested for efficacy. As such, Congress's intent for the FDA did not conflict with state law tort principles requiring drug companies to make effective drugs or test for long-term safety; the FDA simply was not making these requirements or involved in policing them. Courts have found that, until the FDA makes a determination regarding a drug, the manufacturer's obligations to make it safe and effective under state standards still apply. See Tucker v. SmithKline Beecham Corp., 2008 U.S. Dist. LEXIS 55919 at *29-31 (S.D. Ind. July 18, 2008). With DES, there was no new determination that could have possibly made the FDA's position conflict with state law liability; the only time the FDA acted was to contraindicate DES.

The FDA is a reactive, not proactive, agency when it comes to drug safety; the FDA does not ferret out adverse effects for itself, but waits for drug companies to provide that information. When the makers of DES buried the studies adverse to DES and failed to provide the FDA with further information, those manufacturers made the further investigation of DES less likely. Government bureaucracies make mistakes; mistakes are inherent in the system. When such mistakes happen, thousands suffer. Giving the FDA's ignorance of the dangers of DES, pre-emptive power would reward the drug houses for their negligence in the face of administrative failure.

III. THERE IS NO RECOURSE FOR DES DAUGHTERS WITHOUT RESORT TO SUIT; THE FDA'S ENFORCEMENT POWERS CANNOT APPROACH ADEQUATE COMPENSATION

At least one industry advocate before this Court sharing Petitioner's views claimed that there "are remedial mechanisms still available to the FDA" and that the FDA has "pretty broad remedial authority and that it extends to some form of restitution to the victims," and as such, pre-emption of tort suits does not leave victims of drugs such as DES daughters without remedy. See Transcript of Oral Arguments, pg. 55, Warner-Lambert v. Kent, No. 06-1498 (S. Ct. 2008) (Carter G. Phillips, Esq., for the petitioner in that case). Obviously, this deception was meant to convince the Court of an adequate alternative to the tort system. Any claim that the FDA can provide restitution to victims is ludicrous and misleading. Mr. Phillips knows better. When a DES daughter finds out that she is infertile or requires reproductive assistance, she is often on her own to seek compensation for treatment. Even presuming that the FDA might, despite having failed to do so for three decades, pursue the manufacturers of DES for their crimes in misbranding and over-promoting the drug, the sanctions allowed to the FDA are, when available, paltry, and completely insufficient to compensate the injured party.

If a drug company violates 21 U.S.C. § 331 and 332, the FDA may seek restitution for the victims of the mislabeling, but such repayments are not guaranteed. See United States v. Purdue

Frederick Co., 495 F. Supp. 2d 569, 574 (W.D. Va. 2007) (denial of restitution to insurers for misbranding of Oxycontin); see also United States v. Lane Labs-USA, Inc., 427 F.3d 219, 223 (3d Cir. 2005) (Government *may* ask a court for restitution). Restitution under civil principles of equity is limited to reimbursement of the purchase price and potential disgorgement of profits. See Lane Labs, 427 F.3d at 222. Neither a refund of the purchase price nor disgorgement of profits would ever come close to compensating a single victim for cancer, hysterectomy, or infertility.

Conceivably, the FDA could also seek restitution through 18 U.S.C. § 3663,[2] but this method first requires the government to charge the manufacturers of DES with a felony, a step unlikely to occur for pragmatic reasons, and obtain a conviction, where the burden of proof is far greater than in a civil suit. Even if such a conviction were obtained, the damages would be limited. The Eleventh Circuit holds that criminal restitution must be limited to medical bills only. See United States v. Husky, 924 F.2d 223, 227 (11th Cir. 1991). This leaves the infertile DES daughter without compensation for *in vitro* fertilization, assisted reproductive therapy, adoption expenses, surrogacy expenses, and all claims of pain and suffering. In interpreting 18 U.S.C. § 3663 with regard to the

[2] In fact, the First Circuit denies equitable restitution for medical device cases and only provides restitution with a felony conviction. See Talbott v. C.R. Bard, Inc., 63 F.3d 25, 31 (1st Cir. 1995). It is likely that, at least in the First Circuit, civil restitution is unavailable to the FDA for victims of defective drugs.

related field of medical devices, the Third Circuit held that "[t]he act does not permit the FDA to require companies to compensate victims for their medical expenses or for the pain and suffering resulting from a device failure." Michael v. Shiley, Inc., 46 F.3d 1316, 1321 (3d Cir. 1995).

IV. DES DAUGHTERS HAVE RELIED ON TORT COMPENSATION FOR OVER THIRTY YEARS; ANY PRE-EMPTIVE POWER OF THE FDA'S CONSIDERATION SHOULD NOT BE GIVEN RETROACTIVE EFFECT

For the last thirty years, thousands of injured DES daughters have received tort compensation from the manufacturers of DES and their insurers for their costs, including reproductive assistance such as *in vitro* fertilization, adoption, or surrogacy. Those DES daughters who suffer from cancer have also received compensation for their medical bills.[3] To deny the remaining daughters and sons whose claims have not yet materialized from similar compensation based on the findings of the FDA over fifty-five years ago insulates drug manufacturers from obligations all have acknowledged they have had for decades.

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[3] The medical costs of cancer can be ruinous even to a family with insurance; in 2001, half of all bankruptcy filings were in part due to medical bills, even though 75% of those bankrupt had medical insurance. See David U. Himmelstein, et al., "Illness And Injury As Contributors To Bankruptcy," MarketWatch, available at http://content.healthaffairs.org/cgi/reprint/hlthaff.w5.63v1.pdf (Feb. 2, 2005).

This Court, in Chevron Oil Co. v. Huson, 404 U.S. 97 (U.S. 1971), established three principles for when precedents should be applied retroactively: 1) the decision must establish a new rule of law, 2) whether retrospective application will forward or impede the efforts of justice, taking into account the prior history of the rule, and 3) whether inequity will result from retroactive application of the rule. See 404 U.S. at 106-7. In this case, all of these aspects are in favor of prospective application (should pre-emption be applied, which this *amicus* opposes) and allowing DES daughters to continue their efforts for compensation.

Any ruling in favor of pre-emption would express a new principle of law. This Court has been explicit that it has not yet ruled on the FDA's pre-emption of pharmaceutical products cases. See Reigel v. Medtronic, Inc., 128 S. Ct. 999, 1009 (2008) ("It has not been established . . . that no tort lawsuits are pre-empted by drug or additive approval under the FDCA.").

Second, retroactive application will not promote the efforts of justice. DES's placement on the market for use in pregnancy and its maintenance on the market was the product not just of the FDA's oversight, but of continued negligence and willful blindness by the companies who made it. DES manufacturers systematically ignored and suppressed contrary information, see Appendix 1, to continue selling their product in a dangerous manner. Justice is not promoted by papering over their negligence.

Third, "prospective safeguards do not affect the inequities of retroactive application." American Trucking Ass'n v. Smith, 496 U.S. 167, 183 (U.S. 1990). The creation of a class of DES haves and have nots should militate against retroactive application of any pre-emption doctrine. This is true not just for DES but for the scores of other demonstrably defective drugs where many have rightfully recovered for their injuries but others similarly situated will not.

CONCLUSION

When a person is mugged in front of a sleeping policeman, the policeman's virtual presence but inaction does not vitiate the culpability of the mugger nor does it ratify the robbery. The FDA's culpability for DES was being asleep at the switch while drug companies sold a known teratogen to pregnant women. The goals of tort law, are different from the goals of the FDA, and without express pre-emption by Congress, it cannot be assumed that the FDA is the sole recourse for the DES-exposed, especially since the FDA is unable to compensate their injuries.

For the reasons stated above, DES Action requests that this Court affirm the decision of the Supreme Court of Vermont.

RESPECTFULLY
SUBMITTED,

/s/

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APPENDIX 1

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

1932:
A. Lacassagne, "Apparition de Cancers de la Mamelle Chez la Souris, Male, Soumise & DES Injections de Foliculine," 195 Compte Rendu Hebdomadaires de Séance et Memoires de la Societe de Biologie 630 (1932)
Summary: Estrogens induced mammary cancer in mice.

1933:
Milton Overholser and Edgar Allen, "Ovarian Hormone and Traumatic Simulation of Monkey's Cervix to a Condition Resembling Early Cancer," 30 Proceedings of the Soc. for Experimental Biology and Med. 353 (1932)
Summary: Ovarian hormones stimulate a monkey's cervix in a way similar to cancer.

1936:
Gardner, et al., "Cancer of the Mammary Glands Induced in Male Mice Receiving Estrogenic Hormone," 21 Archives of Pathology 265 (1936)
Summary: Estrogen causes cancer of the mammary glands in female mice.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

1936:
Frederick Hisaw and Frederick Ledrugm, "Squamous Metaplasia in the Cervical Glands of Endocrinology in the Monkey Following Oestrin Administration," 20 Endocrinology 228 (1936)
Summary: Estrogen induces squamous metaplasia in a monkey's cervix.

1939:
C.L. Buxton and Earl Engle, "Effects of the Therapeutic Use of Diethylstilbestrol," 113 J. Am. Med. Ass'n 2318 (1939)
Summary: Expressed concerns of diethylstilbestrol's toxic effect.

Charles Geschickter, "Mammary Carcinoma in the Rat with Metastasis in the Rat with Metastasis Induced by Estrogen," 89 Science 35 (1939)
Summary: Estrogen induces mammary cancer in rats.

1940:
Michael B. Shimkin and Hugh G. Grady, "Carcinogenic Potency of Stilbestrol and Estrone in Strain C(3)H Mice," 1 J. Nat'l Cancer Inst. 119 (1940)
Summary: DES possesses the same ability as other estrogens to induce mammary cancer in mice.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

Hugh Auchinloss and Cushman Haagensen, "Cancer of the Breast Possibly Induced by Estrogenic Substance," 114 J. Am. Med. Ass'n 1517 (1940)
Summary: Four cases of breast cancer in humans from exposure to estrogens.

S. Zuckerman, "The Histogenesis of Tissues Sensitive to Oestrogens," 15 Biol. Rev's Cambridge Phil. Soc. 231 (1940)
Summary: Estrogen stimulates endometrial and metaplasic changes in rats.

1945:
J.S. Henry, "Avoidance of Untoward Effects of Oestrogenic Therapy in Menopause," 53 Canadian Med. Ass'n 31 (1946)
Summary: Notes malignant endometrial changes in humans from estrogen therapy.

1947:
S.B. Gusberg, "Precursors of Corpus Carcinoma Estrogens and Adenomatous Hyperplasia," 54 Am. J. Obstetrics and Gynecology 312 (1947)
Summary: Adenomatus hyperplasia of the endometrium, another malignancy in humans caused by estrogens.

TABLE A

Publications Regarding the Carcinogenic Properties of Estrogens Such as DES

Gordon Rosenblum and Eugene Melinkoff, "Preservation of Threatened Pregnancy With Particular Reference to the Use of Diethylstilbestrol," 55 Western J. of Surgery, Obstetrics, & Gynecology 597 (1947)

Summary: "Can diethylstilbestrol in any way affect the glandular balance of the child *in utero*?"

1948:

O.M. DeVaal, "Experimentally Induced Intersexuality in Mice," 1 Acta Endocrinology 319 (1948)

Summary: Cornification of vaginal tissue in mice caused by estrogens.

1949:

A. Vass, "Occurrence of Uterine Fundus Carcinoma After Prolonged Estrogen Therapy," 58 Am. J. Obstetrics and Gynecology 748 (1949)

Summary: Two cases of cancer of the uterine fundus in humans related to estrogen therapy

TABLE B

Publications Regarding the Ability of Drugs Such as DES to Cross the Placenta and Effect Offspring *In Utero*

1937:
William R. Lyons, "The Hormonal Basis of Witches Milk," 37 Proceedings of the Society for Experimental Biol. and Med. 207 (1937)
Summary: Estrogen given to mother found in placenta and in infant.

1939:
Harold Speert, "The Placental Transmission of Sulfanilamide and its Effects Upon the Fetus and Newborn," 66 Bulletin of Johns Hopkins Hosp. 139 (1939)
Summary: Sulfanilamide given to pregnant rats caused the death of their fetuses.

1945:
L.J. Davis and William Forbes, "Thiouracil in Pregnancy: Effect on Fetal Thyroid," 11 Lancet 740 (1945)
Summary: Fetuses of pregnant rats given Thioracil exhibited same symptoms as adult rats exposed to the drug.

TABLE B

Publications Regarding the Ability of Drugs Such as DES to Cross the Placenta and Effect Offspring *In Utero*

1947:
C.D. Larsen, et al., "Pulmonary-Tumor Induction by Transplacental Exposure to Urethane," 8 J. Nat'l Cancer Inst. 63 (1947)
Summary: Urethane given to pregnant rats caused lung cancer in their offspring.

1948:
L.B. Flexner, et al., "The Permeability of the Human Placenta to Sodium in Normal and Abnormal Pregnancies and the Supply of Sodium to the Human Fetus as Determined With Radioactive Sodium," 55 Am. J. Obstetrics and Gynecology 469 (1948)
Summary: Radioactive sodium given to a pregnant woman is found in the placenta and the fetus.

TABLE C

Publications Regarding the Ability of Drugs Such as DES to Cause Sexual Tract Abnormalities in Those Exposed *In Utero*

1930:
R. Courrier, "Rechereches Sur le Mecanisme de la Crise Genitale du Nouve-Ne," Proceedings of the Second Int'l Congress for Sex Research 353 (1931)
Summary: The offspring of guinea pigs injected with estrone during pregnancy exhibited intersex characteristics.

1939:
R.R. Greene, et al., "Experimental Intersexuality: Modification of Sexual Development of the White Rat with Synthetic Estrogen," 41 Proceedings of the Soc. for Experimental Biol. and Med. 169 (1939)
Summary: DES deformed the sexual organs of female rats exposed to the drug.

R.R. Greene, et al., "Experimental Intersexuality: The Paradoxical Effects of Estrogen on the Sexual Development of the Female Rat," 74 Anatomical Record 429 (1939)
Summary: Estrogens malformed the reproductive systems of female rats.

1944:
R.R. Greene, "Embryology of Sexual Structure and Hermaphroditism," 4 J. Clinical Endocrinology 335 (1944)
Summary: Links hormonal imbalance in mammals to hermaphrodism.

TABLE C

Publications Regarding the Ability of Drugs Such as DES to Cause Sexual Tract Abnormalities in Those Exposed *In Utero*

1947:
Karl J. Karnaky, "Estrogenic Tolerance in Pregnant Women," 53 Am. J. Obstetrics and Gynecology 312 (1947)
Summary: Baby girls exposed to DES *in utero* exhibited darkening of the nipples and labia.

1948:
O.M. DeVaal, "Experimentally Induced Intersexuality in Mice," 1 Acta Endocrinology 319 (1948)
Summary: Estrogens will cause vaginal cornification in mice as well as other urogenital and uterine anomalies.

1950:
Robert K. Enders, et al., "Mink Production in Relation to Stilbestrol," 16 The Fur J. 4 (1950)
Summary: DES given to mink prevented them from producing offspring.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

1947:
M.E. Davis and N.W. Fugo, "Effects of Various Sex Hormones on Excretion of Pregnandiol Early in Pregnancy," 65 Proceedings of the Soc. Experimental Biol. and Med. 39 (1947)
Summary: Could not reproduce the reported efficacy of DES; found no benefit from DES administration during pregnancy.

1949:
I.F. Somerville, et al., "Effect of Diethylstilbestrol of Urinary Excretion of Pregnandiol and Endogenous Estrogen During Pregnancy," Lancet, April 23, 1948, at 680
Summary: Found no favorable change in hormonal balance from the prescription of DES during pregnancy.

1950:
Edward M. Davis and Nicholas W. Fugo, "Steroids in the Treatment of Early Pregnancy Complication," 142 J. Am. Med. Ass'n 778 (1950)
Summary: Questioned the value of DES as a miscarriage preventative.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

E.D. Colvin, et al., "Salvage Possibilities in Threatened Abortion," 59 Am. J. Obstetrics and Gynecology 1208 (1950)

Summary: Found that prophylactic use of DES was wholly unwarranted and that bed rest and sedation are the only effective treatments of threatened miscarriage.

R.E. Crowder, et al., "The Management of Threatened Abortion: A Study of 100 Cases," 60 Am. J. Obstetrics and Gynecology 896 (1950)

Summary: Found that DES does not stimulate the body to produce new hormones of its own and therefore there is no basis for the use of DES in preventing miscarriage.

Ralph A. Reis, et al., "The Management of the Pregnant Diabetic Woman and Her Newborn Infant," 60 Am. J. Obstetrics and Gynecology 1023 (1950)

Summary: Stated that it was "unnecessary" to subject pregnant women to DES.

1952:

David Robinson and Landrum Shettles, "The Use of Diethylstilbestrol in Threatened Abortion," 63 Am. J. Obstetrics and Gynecology 1330 (1952)

Summary: Complete failure of DES to prevent miscarriage.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

Paul Pedowitz and Edmund L. Shievin, "The Pregnant Diabetic," Bulletin of the New York Academy of Medicine 440 (1952)
Summary: Found that substitutional hormonal therapy, such as DES therapy, was not warranted.

1953:
Arthur King, "Threatened and Repeated Abortion: Present Status of Therapy," 1 Obstetrics and Gynecology 104 (1953)
Summary: Analyzed the studies purporting to show that DES was effective; found instead that studies were without adequate controls and did not rule out random chance as the reason for the positive results.

James Henry Ferguson, "The Effect of Stilbestrol on Pregancy Compared to the Effect of a Placebo," 65 Am. J. Obstetrics and Gynecology 592 (1953)
Summary: DES has no effect on fetal survival.

W.J. Dieckmann, et al., "Does the Administration of Diethylstilbestrol During Pregnancy Have Therapeutic Value?" 66 Am. J. Obstetrics and Gynecology 1062 (1953)
Summary: First double-blind, prospective study of DES in preventing miscarriage. DES did not reduce the number of miscarriages.

TABLE D

Studies Finding DES of No Use in Preventing Miscarriage

1955:

Louis Sanford Goodman, et al., The Pharmacological Basis of Therapeutics (2d ed. 1955)

Summary: "Certainly the available evidence does not justify the routine use of estrogen in the treatment of threatened abortion or as a prophylactic against the pregnancy."